REMARKS

Claims 1, 3-5, 8, 9, 11-15, 17-32, 44-55, 57-62, 64, 65 and 67-99, are pending in this application, of which claims 1, 3, 31, 32, 44, 59, 79 and 90 are being amended, and claim 2 is being cancelled.

Applicant thanks the Examiner for withdrawing the Rejection Under 35 U.S.C. 112, second paragraph, in view of Applicant's previous remarks.

The claim amendments are fully supported by the Specification and entry of the amendments is respectfully requested. For example, the amendments to independent claims 1, 31, 32, 44, 59, 79 and 90 are based on claim 2. Claim 3 is being amended to correct its dependency.

Reconsideration of the present rejection is respectfully requested in view of the arguments presented herein and previously submitted Declaration of Dr. Jeffry Weers.

1. Double Patenting Rejection

The Examiner maintained the rejection of claims 1-3, 8-9, 11-15, 17-22, 27-32, 44-55, 59-62, 64-65, and 67-78 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-23, 25, 27-30, 34-37, 41-45 of copending Application No. 09/568,818.

When the present application or the 09/568,818 application is indicated as allowable, the double patenting issue will be addressed in the other application by the filing of a Terminal Disclaimer.

2. Rejection Under 35 U.S.C. § 103(a) of Claims 1-5, 8-9, 11-15, 17-32, 44-55, 57-62, 64-65 and 67-78

The Examiner rejected claims 1-5, 8, 9, 11-15, 17-32, 44-55, 57-62, 64, 65 and 67-99, under 35 U.S.C. § 103 (a), as unpatentable over Weers et al. (6,309,623) in view of Materne et al. (GB 2065659). The rejection is respectfully traversed.

As amended, claim 1 is to a particulate composition for delivery to the pulmonary system, the composition comprising: particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.

Applicant respectfully submits that the Office Action has failed to establish a prima facie obviousness rejection of the claims based on the cited combination of Weers et al. and Materne et al.. To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a), there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings of the different references. Second, there must also be a reasonable expectation of success for such a combination. Also, the prior art references that are combined must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Weers at al. does not teach a particulate composition comprising particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid

crystal transition temperature that is greater than room temperature by at least 20°C, as claimed in claim 1.

Weers et al. teaches selection of a lipid surfactant which already has a gel-to-liquid crystal phase transition temperature of greater than about 40°C, and use of such a surfactant to improve the stability of a respirator dispersion, increase pulmonary deposition, and facilitate the preparation of the suspension. Specifically, Weers et al. teaches:

> "...in particularly embodiments, the structural matrix is associated with, or comprises, a surfactant such as, a phospholipid or fluorinated surfactant. Although not required, the incorporation of a compatible surfactant can improve the stability of the respirator dispersions, increase pulmonary deposition, and facilitate the preparation of the suspension."

(Column 15, line 62 to column 16, line 2.) Weers et al. further teaches that particular lipid surfactants should be selected from other lipids to have a gel to liquid crystal phase transition temperature of greater than about 40° C:

> "Lipids, including phospholipids, from both natural and synthetic sources are particularly compatible with the present invention and may be used in varying concentrations to form the structural matrix. Generally, compatible lipids comprise those that have a gel to liquid crystal phase transition greater than about 40° C.

(Column 16, lines 44-49). Thus, Weers et al. teaches use of surfactant lipids to improve properties of the particles, and teaches that such lipid surfactants should that have a gel to liquid crystal phase transition temperature of greater than about 40°C.

The difference between the teachings of the Weers et al. patent and the instant Specification is explained by the first named inventor of the Weers et al. patent, Dr. Jeffry G. Weers, in paragraphs 9-16 of the attached Declaration (Weers Declaration). This Declaration should be given particular weight because the Declarant is an inventor of both the present application as

well as the cited Weers et al. patent.

As explained in the Declaration, Weers et al. teaches that the problem of the low transition temperature of phospholipids is easily solved by selecting only those phospholipids which have high gel to liquid transition temperatures above 40°C. By teaching selection of a phospholipid having a minimum gel to liquid crystal phase transition temperature of 40°C, Weers et al. reference teaches away from the more complicated solution of chemically altering a phospholipid with a polyvalent cation to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation to obtain a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C, as claimed. If phospholipids having a gel-to-liquid crystal transition temperatures exceeding room temperature by 20°C, for example the 40°C minimum temperature taught by Weers et al., can be easily obtained by simply selecting the right phospholipid, one of ordinary skill in the art would not be motivated to experimentally determine a suitable compound, or a ratio of the same compound to phospholipid to change the gel-to-liquid crystal transition temperature of phospholipid to reach temperatures above room temperature. Selection of the phospholipid having the right minimum temperature should suffice. Thus, Weers at al. would not provide any motivation to one of ordinary skill in the art to try to modify the structure of a phospholipid to obtain a higher gel to liquid transition temperature, because such modification is not taught, or is even taught as unnecessary because it is solved through selection.

In fact, the Office Action acknowledges that Weers et al. lacks an exemplification of a composition comprising saturated phospholipid and divalent cation. The Office Action also acknowledges that Weers et al. does not teach the claimed ratio of polyvalent cation to phospholipid of at least 0.05. More importantly, Weers et al. also does not teach or suggest that use of a polyvalent ion in the claimed minimum molar ratios achieves the surprising result of changing its gel-to-liquid transition temperature of a phospholipid. Instead, as acknowledged by the Examiner, Weers et al. teaches that an inorganic salt such as calcium chloride can be added to, for example, to adjust the

pH of the feedstock. Weers et al. does not teach or suggest that phospholipid can be chemically modified by a polyvalent cation to have a gel to liquid crystal phase transition temperature that is higher than that of the unmodified phospholipid. Thus the Office Action is ignoring the language of the claim taken as a whole. Clearly, one of ordinary skill in the art would not have the motivation to devise the more difficult solution of increasing a gel-to-liquid transition temperature of a particular phospholipid by chemically modifying its structure, when Weers et al. teaches that such a compatibility problem is easily solved simply by selecting a particular phospholipid from commercially available phospholipids.

"In making the assessment of differences between the prior art and the claimed subject matter, section 103 specifically requires consideration of the claimed invention 'as a whole.'" Princeton Biochemicals, Inc. v. Beckman Coulter, Inc. (Fed. Cir., No. 04-1493, 6/9/05). "[S]imply identifying all of the elements in a claim in the prior art does not render a claim obvious. Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1275 (Fed. Cir. 2004). Instead section 103 requires some suggestion or motivation in the prior art to make the new combination. In re Rouffet, 149 F.3d 1350, 1355-56 (Fed. Cir. 1998).

Weers et al. does not suggest that a polyvalent cation can be used to increase gel-to-liquid transition temperature of a phospholipid, and does not suggest that such a combination is desirable to achieve a higher gel-to-liquid transition temperature. Nor does Weers et al. teach the claimed molar ratio recited in the present claim, or that ratios above the claimed minimum ratio can increase the gel-to-liquid transition temperature of phospholipid to exceed room temperature by 20°C. Thus, Weers et al. provides no teaching or suggestion to derive the claimed particles as recited in claim 1.

Materne et al. does not make up for the deficiencies of Weers et al. because Materne et al. also does not teach the claimed invention as a whole. Weers et al. provides no teaching or suggestion to one or ordinary skill in the art to seek a reference such as Materne et al.. Further, Materne et al. does not make up for the

deficiencies of Weers et al., because Materne et al. does not teach or suggest that a polyvalent ion in the claimed minimum molar ratios of 0.05, when added to phospholipid, achieves the surprising result of forming particles having a gel-to-liquid transition temperature that exceeds room temperature by 20°C.

Materne et al. teaches preparation of calcium phosphatidycholine chloride by the addition of calcium chloride to an unsaturated phospholipid. As explained in paragraphs 17-19 of the Weers Declaration, the description of the physiochemical properties and appearance of the phospholipids taught by Materne et al. corresponds to unsaturated phosphatidylcholines. For example, Materne et al. teaches that phosphatidylcholines are plastic materials of low stability which are difficult to process and handle. Materne et al teaches:

> ...The eluate is then evaporated giving substantially pure phosphatidylcholine. However, the phosphatidylcholine produces in this manner shows some considerable disadvantages. It is obtained as a plastic material which has low stability and is difficult to further process and handle. Therefore, various efforts have been made to convert this plastic material into a free flowing powder or a liquid of low viscosity by the addition of various auxiliary agents.

(Page 1, lines 36-45.) As explained by Dr. Weers, such a description corresponds to particles of unsaturated phosphatidylcholines which fuse into large conglomerates due to temperature or moisture induced aggregation. (Para 17, Weers Declaration.) In contrast, saturated phosphatidylcholines arrive from vendors as flowable powders which are typically chemically stable because they contain no double bonds that can be oxidized; thus, these materials are not difficult to handle under ambient conditions. Materne et al. further describes the phosphatidylcholines as being yellow in color (see Example 1), which is also indicative of oxidation processes involving double bonds present in unsaturated materials. In contrast, saturated phosphatidylcholines are generally white in appearance. (Paragraphs 18-19, Weers Declaration.)

Furthermore, Materne et al. does not teach a particulate composition comprising particles in which the gel-to-liquid transition temperature is increased to

temperatures that exceed room temperature by 20°C, by the addition of a specific molar ration limit of a polyvalent ion to phospholipid. Materne et al. teaches that the calcium phosphatidylcholine chloride prepared by the described method, is of high purity, can be processed more readily, and has high stability. Materne et al teaches:

> The new calcium phosphatidylcholine chloride which is produced by the present process furthermore may be processed more readily than pure phosphatidylcholine. It is a powder or granular product characterized by a high stability and may be readily used for pharamaceutical preparations in view of its high phosphatidylcholine content prepared by the described method, is of high purity, can be processed more readily and has high stability.

(Page 1, lines 123-129.) Materne et al further teaches preparation of such a new calcium phosphatidylcholine chloride in Example 1 and then teaches that "[a}fter dissolving the product in choloform and evaporating the product, the product shows unchanged analytical data." (Example 1, page 2, lines 19-35.) Thus, Materne et al, teaches that the calcium addition promotes <u>chemical stability</u> of the product because it does not change when dissolved in various solvents. Materne et al. does not teach a particles in which the gel-to-liquid transition temperature is increased to temperatures that exceed room temperature by 20°C, by the addition of a specific molar ratio limit of a polyvalent ion.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. §103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. <u>Stratoflex, Inc. v. Aeroquip Corp.</u>, 713 F. 2d 1530, 218 USPQ 871 (Fed. Cir. 1983). The benefits of the claimed invention should be viewed without the benefit of impermissible hindsight vision afforded by the claims themselves.

Materne et al. does not teach the claimed invention as a whole, because Materne et al. does not teach that a ratio of polyvalent cation to phospholipid of at least 0.05 achieves the surprising result of changing the gel-to-liquid transition temperature of particles incorporating the same, to temperatures that exceed room temperature by

20°C. Instead, Materne suggests that calcium addition improves the chemical stability of the composition and not the gel-to-liquid temperature. Furthermore, Materne et al. teaches the use of unsaturated phospholipids and not saturated phospholipids, and provides no motivation for substituting a saturated phospholipid for the described unsaturated phospholipid. Accordingly, there would have been no motivation to substitute the unsaturated phospholipids taught by Materne et al. with the claimed saturated phospholipids. Thus, Materne et al. does not cure the deficiencies of Weers et al., and the cited combination fails to establish a prima facie obviousness rejection.

Furthermore, the surprising and unexpected results of the claimed invention refute the obviousness rejection. The instant claims are to particles comprising saturated phospholipids in combination with a polyvalent cation in a molar ration that increases the gel to liquid transition temperature of the particles. As explained by Dr. Weers, the addition of calcium chloride to a saturated phospholipid as claimed, provides an unexpected increase in gel to liquid crystal transition temperature. (Paragraphs 6-8, Weers Declaration.) The inventive aspect of particles comprising a saturated phospholipid in combination with a polyvalent cation in a particular molar ratio to provide a higher gel to liquid transition temperature is an unexpected result negating the rejection of obviousness. The unexpected increase in Tm of saturated phospholipids, such as DSPC and DDPC, with the addition of polyvalent ion is shown in Tables Ib and Ic below, which are found on page 23-24 of the Specification:

Table Ib (DSPC)

Ca/DSPC (mol/mol)	Tm (°C)
0(hydrated)	58
0	79
0.25	85
0.5	98
1.0	126

Table Ic (DPPC)

Ca/DSPC (mol/mol)	Tm (°C)
0(hydrated)	42
0	63
0.25	69
0.5	89

Furthermore, it is surprising that the addition of a polyvalent ion, such as

divalent calcium, would affect the Tm of a phospholipid. It is even more surprising that the addition of a polyvalent cation, for example, in the form of a highly hygroscopic salt such as calcium chloride, would stabilize a dry powder prone to moisture induced destabilization, as one would expect that calcium chloride would readily absorb water and lead to particle aggregation. Figure 1 in the Declaration of Dr. Weers shows a dynamic vapor adsorption (DVS) graph that plots the change in %mass for increasing molar ratio of DSPC to calcium chloride, which shows that unexpectedly, particles containing calcium had about the same moisture absorption properties as particles without calcium. It is believed that as the ratio of amount of calcium polyvalent ion to phospholipid was increased to the claimed 0.5:1 ratio, the polyvalent calcium ion modifies the structure of the phospholipid thereby no longer existing as hydroscopic calcium chloride. It is further believed that the calcium ions intercalate the phospholipids membrane to interact directly with the negatively charged portion of the saturated headgroup of the phospholipid resulting in the dehydration of the head group and condensation of the acryl-chain packing, all of which leads to the increased thermodynamic stability of the phospholipid, as explained at page 8, lines 24-28 of the instant Specification. The unexpected and substantially increase in gel-to-liquid transition temperature of the particles provided numerous benefits including better storage stability of the powders, improved dispersibility, reduced likelihood of absorbing atmospheric water, better lung distribution, and improved emitted dose and fine particle fraction.

Thus, the cited combination of Weers et al. and Materne et al. simply does not sustain a prima facie obviousness rejection of claim 1, which recites a saturated phospholipid, a polyvalent cation, and a molar ratio of the two compounds that is higher than 0.5 to increase the gel to liquid transition temperature of the phospholipid containing particle. For these reasons, claim 1 and its dependent claims are patentable under Section 103 over Weers et al. and Materne et al..

Claim 31

Claim 31 is to a particulate composition comprising particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and wherein the particles have a gel-to-liquid transition temperature at least 20°C higher than room temperature.

Claim 31 and the claims dependent therefrom, recite that the molar ratio of polyvalent cation to phospholipid is at least 0.05 and that the particles have a gel-to-liquid transition temperature at least 20°C higher than room temperature, and thus, are patentable over Weers et al. and Materne et al. for the same reasons as recited above, and to avoid repetition, will not be repeated.

Claims 32, 44 and 59

Claim 32 is to a particulate composition for delivery to the pulmonary system, the composition comprising porous particles comprising: 20 – 99.9% of a saturated phospholipid; a polyvalent cation; and 0.1 – 80% active agent; wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.

Claim 44 is to a method of delivering an active agent to a patient in need thereof, the method comprising administering to the respiratory tract of the patient an effective amount of particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.

Claim 59 is to a particulate composition comprising particles comprising a structural matrix comprising a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation, and to obtain particles having a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C, and wherein the particles further comprise an active agent.

Claims 32, 44 and 59, and the claims dependent therefrom, all recite inter alia, that the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C, and thus, are patentable over Weers et al. and Materne et al. for the same reasons as recited above.

Claims 72-78

Claims 72-78 are further patentable over Weers et al. and Materne et al., because the cited references do not teach a particulate composition comprising a saturated, zwitterionic phospholipid as taught in claims 72-74, 77, and 78, nor do the cited references teach hollow particles as claimed in claim 76. For these reasons, claims 72-78 are independently allowable over the cited references.

Claim 79

Claim 79 is to a particulate composition for delivery to the pulmonary system, the composition comprising particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and less than 2, whereby the gel-to-liquid crystal transition

temperature of the particles is higher than particles without the polyvalent cation, and is greater than room temperature by at least 20°C.

Claim 79, and the claims dependent therefrom, are patentable over Weers et al. and Materne et al., because the cited references do not teach a molar ratio of polyvalent cation to phospholipid is at least 0.05 and less than 2, whereby the gel-to-liquid crystal transition temperature of the particles is higher than particles without the polyvalent cation, and is greater than room temperature by at least 20°C. The reasons and arguments supporting the same are recited above.

Claim 90

Claim 90 is to a method of making a temperature stable particulate composition for delivery to the pulmonary system, the method comprising: forming a feedstock comprising a saturated phospholipid emulsion and an active agent; adding a polyvalent cation to the feedstock in an amount sufficient to provide a molar ratio of polyvalent cation to phospholipid in the feedstock that is at least 0.05 and less than 2; and drying the polyvalent cation containing feedstock to form porous particles having a gel-to-liquid crystal transition temperature that is higher than a storage room temperature of the porous particles by at least about 20° C.

Claim 90, and the claims dependent therefrom, are also patentable over the cited references because the references do not teach a method of making a temperature stable particulate composition comprising the step of adding a polyvalent cation to the feedstock in an amount sufficient to provide a molar ratio of polyvalent cation to phospholipid in the feedstock that is at least 0.05 and less than 2, and drying the polyvalent cation containing feedstock to form porous particles having a gel-to-liquid crystal transition temperature that is higher than a storage room temperature of the porous particles by at least about 20° C.

The above-discussed amendments are believed to place the present application in condition for allowance. Should the Examiner have any questions regarding the above remarks, the Examiner is requested to telephone Applicant's representative at the number listed below.

Respectfully submitted,
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